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IKAP is a scaffold protein of the IkappaB kinase complex.

Cohen L, Henzel WJ, Baeuerle PA.

Tularik Inc., South San Francisco, California 94080, USA.

The transcription factor NF-kappaB coordinates the activation of numerous genes in response to pathogens and pro-inflammatory cytokines, and is, therefore, vital in the development of acute and chronic inflammatory diseases. NF-kappaB is activated by phosphorylation of its inhibitory subunit, IkappaB-alpha, on serine residues 32 and 36 by cytokine-activated IKB kinases (IKKs); this phosphorylation precedes rapid degradation of IkappaB. IKK-alpha and IKK-beta isozymes are found in large complexes of relative molecular mass 700,000-900,000 (M(r) 70K-90K), but little is known about other components that organize and regulate these complexes. IKK-alpha was independently discovered as a NF-kappaB-inducing kinase (NIK)-associated protein in a yeast two-hybrid screen, and IKK-beta was also identified by homology screening. It is, however, unknown whether NIK is part of the IKK complex. Here we isolate large, interleukin-1-inducible IKK complexes that contain NIK, IKK-alpha, IKK-beta, IkappaB-alpha, NF-kappaB/RelA and a protein of M(r) 150K. This latter component is a new protein, termed IKK-complex-associated protein (IKAP), which can bind NIK and IKKs and assemble them into an active kinase complex. We show that IKAP is a scaffold protein and a regulator for three different kinases involved in pro-inflammatory cytokine signalling.

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